REMARKS

Upon entry of the foregoing amendments, allowed claims 33, 34 and 49-52, amendments of currently rejected claims 54, 55 and 57-60, and new claim 61 will be pending. Claims 33, 59, 60 and 61 are the only pending independent claims.

Explanation of and Support for the Amended and New Claims

Claims formerly numbered 60 and 61 have been renumbered as claims 59 and 60, since claim number 59 was inadvertently skipped in the last Amendment filed December 31, 2007. As a result, the dependency of claims 54 and 57 have been amended to depend from, respectively, renumbered claims 59 and 60.

The Examiner has noted several times in the outstanding Office Action that claims 59 and 60 did not functionally limit the scope of these variant claims. Claims 59 and 60 have been amended, and new claim 61 has been drafted to include the appropriate functional language so as to recite that each of the isolated protein variant and the isolated protein, respectively, is immunogenetic. These amendments are supported at least at page 13, lines 5-12, of the application as filed. New independent claim 61 is added to provide a claim covering an immunogenic isolated protein having at least 90% homology to SEQ ID NOs:23 or 35. The immunogenicity is supported at least at page 13, lines 5-12, of the application as filed. The homology of at least 90% is supported at least at page 15, lines 11-13. Also, the following tables show the homology between other exemplary sequences and SEQ ID NOs:23 and 35 based on an analysis of the respective sequence listings.

Comparison	% identity
SEQ ID NO: 23 vs 24	95
SEQ ID NO: 23 vs 27	93
SEQ ID NO: 23 vs 35	90

Comparison	% identity
SEQ ID NO: 35 vs 23	90
SEQ ID NO: 35 vs 26	93
SEQ ID NO: 35 vs 36	95
SEQ ID NO: 35 vs 39	93

Applicants submit that the claim amendments do not include new matter and are supported by the originally filed specification. Entry of the claim amendments is respectfully requested.

The Examiner is reminded that there are no outstanding prior art rejections.

The Office Action contains rejections to claims 54, 55 59 and 60 under 35 USC §112, first paragraph, based on an asserted lack of enablement and a rejection of claims 54, 55 and 57-60 under 35 USC §112, first paragraph, based on an asserted lack of an adequate written description.

Applicants respectfully traverse these rejections. Independent claims 59-61, and their dependent claims 54, 55, 57 and 58 are allowable for at least the following reasons.

35 USC §112 Enablement

The Examiner has rejected former claims 60 and 61 (now renumbered as claims 59 and 60) as lacking enablement.

As an initial comment, the Examiner has referred to previous submissions using language that in the Examiner's view "indicate that the Applicant is uncertain about the function of the claimed genus.....". Also, at various places in the Office Action, the Examiner noted that former claims 60 and 61 did not recite a functional limitation rejection that would put any functional constraint on the variants encompassed by such claims.

As noted above, renumbered claims 59 and 60 have been amended and new claim 61 all now recite that the variant protein is immunogenic. In view of this recitation, there is 100% certainty that variants encompassed by these claims will indeed be immunogenic. Accordingly, it is submitted that claims 59 and 60 and also new claim 61 only encompass variants that retain immunogenicity.

More particularly, claim 59 encompasses variants where a variable (V) region amino acid is conservatively substituted without removing immunogenicity. SEQ ID NOs:23 and 35 each comprise about 30-35 V region amino acids (i.e. four V1 amino acids; V3; and V4). Table 2 and the specification at pages 20-25 provide examples of conservative amino acid substitutions that may be expected to retain protein function (*e.g.* immunogenicity).

With regard to claim 60, guidance as to possible amino acid deletions may be found by reference to FIG. 1. With reference, to V3 and V4 in particular, there are only four absolutely

conserved amino acids: A, T in V3 and G, T in V4. It is therefore reasonable to conclude that other, non-conserved residues could be deleted without eliminating immunogenicity.

Mutagenesis of proteins and encoding nucleic acids is extremely well known in the art. The production of such variants is therefore well within the scope of persons skilled in the art without undue experimentation.

Predicting immunogenicity is also well known in the art. As previously explained, there are several predictive methods of defining the immunogenicity of a protein without having to resort to the kind of empirical, undue experimentation referred to by the Examiner.

One method of predicting protein immunogenicity is bioinformatic analysis. Immunogenicity can be predicted by analysis of the probability that a particular region of a protein is exposed on the surface of the protein. This prediction is based on a number of physical characteristics of the protein sequence including: (a) hydrophobicity (Hopp, T.P. and Woods, K.R., 1983, "A computer program for predicting protein antigenic determinants." *Mol. Immunol.* 20, 483–489); (b) the relative occurrence of amino acids in antigenic regions (Welling, G.W., Weijer, W.J., van der Zee, R., and Welling-Wester, S., 1985, "Prediction of sequential antigenic regions in proteins." *FEBS Lett*, 188(2):215-218); and (c) surface accessibility and flexibility (Kolaskar, A. S. and Tongaonkar, P.C., 1990, "A semi-empirical method for prediction of antigenic determinants on protein antigens." *FEBS Lett*, 276(1-2):172-174). Software is readily available that allows these "antigenicity analysis" predictions to be performed. Use of this software would allow determination of which variants of proteins according to SEQ ID NOs:23 or 35 are more likely to be antigenic and thereby represent variants that will be immunogenic.

More specifically, and with respect to claim 60 in particular, Example 10 provides a working Example that shows that deletion of variable region amino acids were indeed performed while retaining immunogenicity.

Firstly, the constructs of Example 6 (SEQ ID NOs:25 and 37) consist entirely of C regions, hence have all V region amino acids deleted. Both proteins were nevertheless immunogenic.

Secondly, SEQ ID NOs:25 and 37 are related to SEQ ID NOs:23 and 35. Each is a PMC21 deletion mutant. SEQ ID NO:25 is SEQ ID NO:23 minus a few V1 amino acids, V3, V4, C3 and C4. SEQ ID NO:35 is SEQ ID NO:37 minus a few V1 amino acids, V3, V4, C3 and C4. All proteins were immunogenic. Accordingly, Example 10 provides a working Example

proving that V region amino acids of SEQ ID NOs:23 and 35 may be deleted while retaining immunogenicity. This also negates the Examiner's view that the Applicants are "uncertain" about the effects of deleting V region amino acids.

Applicants respectfully but strongly submit that there is no undue experimentation required to make and use the invention encompassed by claims 59-61. A person skilled in this art of biotechnology, typically a Ph.D. with some years of experience, would certainly know how to make and use the invention as presently claimed.

Applicants therefore submit that claims 59, 60 and 61 are enabled. Reconsideration and withdrawal of the lack of enablement rejection of claims 59 and 60 are respectfully requested.

35 USC §112 Written Description

The Examiner has repeatedly argued that Applicants have not made a correlation between structure and function that demonstrates that Applicants were in possession of the claimed invention. Further to this, the Examiner has argued that Applicants have not explicitly described any examples of variant proteins falling within the scope of claims 59 and 60. Applicants believe that the Examiner may have overlooked certain aspects of the application. The comments below address this rejection of claims 59 and 60 also in so far as the Examiner may be inclined to view new claim 61 in the same manner.

The specification always asserted that deletion or substitution of V region amino acids would not negatively impact upon immunogenicity. More particularly, the specification asserted that this may in fact assist the elicitation of a cross-protective immune response. This is a correlation between structure and function that was present in the originally-filed specification. Applicants always have been in possession of this invention.

FIG. 1 provides a written description of the variability of amino acid sequences along the entire length of each of ten (10) *N. meningitidis* protein antigens. This constitutes adequate disclosure of a range of examples of possible V region amino acid substitutions (claim 59), deletions (claim 60) and other amino acid sequence variations (claim 61) to SEQ ID NOs:23 and 35 that are available to a skilled person.

More specifically, and as stated previously when considering enablement, Example 10 provides a working Example that shows that deletion of variable region amino acids can indeed be performed while retaining immunogenicity. The constructs of Example 6 (SEQ ID NOs:25

and 37) consist entirely of C regions, hence have all of the V region amino acids deleted. Both proteins were immunogenic. Applicants have therefore demonstrated possession of the claimed invention.

With particular regard to claim 60, SEQ ID NOs:25 and 37 are related to SEQ ID NOs:23 and 35. Each is a PMC21 deletion mutant. SEQ ID NO:25 is SEQ ID NO:23 minus V1 amino acids, V3, V4 , C3 and C4. SEQ ID NO:35 is SEQ ID NO:37 minus V1 amino acids, V3, V4, C3 and C4. All proteins were immunogenic. Applicants have therefore demonstrated possession of the invention of claim 60.

With particular regard to claim 61, SEQ ID NOs:24, 27 and 35 are all at least 90% identical to SEQ ID NO:23. These are specific Examples of proteins falling within the scope of claim 61. In Example 10, SEQ ID NO:35 was shown to be immunogenic.

Furthermore, SEQ ID NOs:23, 26, 36 and 39 are all at least 90% identical to SEQ ID NO:35. These are specific Examples of proteins falling within the scope of claim 61. In Example 10, SEQ ID NO:23 was shown to be immunogenic.

The specification therefore does provide specific Examples of variants falling within the scope of claim 61, demonstrating possession of that claimed invention by Applicants.

Claims 54 and 57 recite a pharmaceutical composition comprising the isolated protein variant of claims 59 and 60, respectively, and a pharmaceutically-acceptable carrier, diluent, or excipient. The specification describes and teaches pharmaceutical compositions comprising a modified NhhA protein. Because the proteins of claims 59 and 60 are fully enabled and described as discussed above, claims 54 and 57 are also fully enabled and described.

Claims 55 and 58 recite that the pharmaceutical composition of claim 54 and 57, respectively, is immunogenic. Because these compositions include the immunogenic protein variant of claim 59 or the immunogenic protein of claim 60, the compositions also are immunogenic. Thus, claims 55 and 58 are also fully enabled and described.

Reconsideration and withdrawal of the lack of written description rejection of claims 54, 55, and 57-60 are respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance. Reconsideration and withdrawal of all of the rejections, and an early Notice of Allowance of all pending claims are respectfully solicited.

Respectfully submitted,

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August 8, 2008
(Date)

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